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ON ADDISON'S DISEASE AND THE FUNCTION OF THE SUPRARENAL BODIES.[1]

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No satisfactory explanation has yet been given of the bronzing of the skin and of the peculiar train of symptoms which frequently accompany disease of the suprarenal bodies, and this is not surprising since anatomists and physiologists can give us no idea as to the function of these organs.

In this paper I have collected certain bits of evidence which may help to advance the inquiry a stage, even if my arguments should fail to convince the critical.

I propose to consider the subject under the following heads: 1, the comparative anatomy and development of the adrenals; 2, their physiological chemistry; 3, theories as to their function; 4, results of spectroscopic examination of the adrenals and of the urine in Addison's disease; and 5, teachings of pathology.

Comparative Anatomy and Development of the Suprarenal Bodies—The great use of the adrenals in the life of animals is proved by their wide distribution among vertebrates; since they are found in mammals, birds, reptiles, amphibians, and fishes.

In fishes they lie on the anterior or posterior surface of the kidneys as small paired or multiple bodies, varying in size from that of a pin's head to that of a bean (Eberth).[2] In elasmobranchs they form a double row of bodies, arranged segmentally, lying on the right and left of the vertebral column, and consist of a mesoblastic and a sympathetic part. They may be wanting in some teleosteans, but when present they sometimes represent the metamorphosed anterior (lymphoid) part of the kidney, and sometimes are closely united with the kidneys. It is probable that in all vertebrates they arise in connection with the pro- or mesonephros (Wiedersheim).[3]

In amphibians they form small yellowish granules, and lie either on the ventral side (Anura) or on the inner side (Urodela) of the kidneys, receiving their blood supply both in amphibians and reptiles from the renal-portal vein (Wiedersheim).

In reptiles the adrenals are of a bright yellow colour, of an elongated or lobulated form, and lie in close contact with the genital glands (Wiedersheim). In batrachians, saurians, chelonians, and birds, the cortical and medullary substances are placed side by side, in rounded heaps or in branched cords or columns (Eberth).

In birds "the weblike arrangement of the branched cortical and medullary columns is still more distinctly marked" (Eberth).

In mammals the suprarenal of each side forms a definite and uniform mass, lying close to the corresponding kidney, and in it an ectodermal (that is, sympathetic) medullary, and a mesodermal cortical substance can always be recognised, the two elements here being closely united together (Wiedersheim).

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[1] Read before the Pathological Section of the Birmingham Branch of the British Medical Association, January 27th, 1888.

[2] Stricker's *Histology*.

[3] *Comparative Anatomy*, Eng. tran., p. 161.

As we ascend the vertebrate scale the adrenals become gradually better developed; the same remark applies to the respiratory pigments. In fishes and amphibians[4] the muscle hæmoglobin, and the myohæmatin are badly developed, in reptiles better, while in birds and in mammals they reach their highest point of development.

It is not my intention to refer to all recent work on the development of the adrenals. I will merely briefly refer to Balfour's researches on the development of the elasmobranch fishes;[5] they are well known. He showed that in these there are "(1) a series of paired bodies derived from the sympathetic ganglia, and (2) an unpaired body of mesoblastic origin. In the amniota these bodies unite to form the compound suprarenal bodies, the two constituents of which remain, however, distinct in their development. The mesoblastic constituent appears to form the cortical part of the adult suprarenal body, and the nervous constituent the medullary part." Mitsukuri[6] has confirmed Balfour's views by studying the development of the adrenals of the rabbit and the rat, and finds that the medullary part arises from the sympathetic ganglia, and the cortical part is of mesoblastic origin; the former at first is outside the cortical part, but becomes gradually enclosed by it, but still retaining some connection with the neighbouring ganglia. Hence we know that the bulk of the adrenal is not of nervous but of mesoblastic origin, for in the adult (mammal) the thinner parts of the organ consist entirely of cortical substance (Schäfer),[7] so that the adult suprarenal may be considered a glandular organ.

Physiological Chemistry of the Adrenals.—Hoppe-Seyler (*Physiologische Chemie*) shows that the medulla of the adrenal contains a substance which is easily changed (by decomposition) after death, and besides albuminous bodies, a substance which is coloured dark blue to blackish green by ferric chloride; carmine-red by oxidising substances such as tincture of iodine, chlorine- or bromine-water; and red by the sub-chlorides of manganese, cobalt, and nickel. The watery extract assumes, by standing exposed to the air, especially if exposed to sunlight, a red colour. On extracting the adrenals with dilute hydrochloric acid, and adding ammonia to the extract, a beautiful red colour is produced. The substance giving these colour changes is soluble in very dilute aqueous acid solutions, insoluble in ether, alcohol, chloroform, bisulphide of carbon and benzol; it has not been isolated, and belongs, according to Virchow, to the fluid bathing the tissue elements. [Krukenberg considers that several chromogens are present in the adrenals.] Cloëz and Vulpian have found hippuric and taurocholic acids and calcium chloride in the adrenals of the sheep, and Seligsohn found benzoic acid and taurin, the latter having also been found by Holm. Külz found inosit in them. I think it is highly improbable that these constituents could have found their way into the organ "by imbibition;" they must be produced in the organ itself. If so a very active downward metabolism must be taking place there.

Theories as to the Function of the Adrenals.—The textbooks agree in stating that we know nothing of the function of the adrenals. In Carpenter's *Physiology* (ninth edition, 1881) it is stated: "Although Brown-Séquard found that ablation of the

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[4] Researches on Myohæmatin and the Histohæmatins, *Philosophical Transactions*, Part I, 1886.

[5] *Treatise on Comparative Embryology*, vol. 2, p. 547-549. *Cf.* Weldon, *Quart. Journ. Micros. Sc.*, 1884 and 1885.

[6] On the Development of the Suprarenal Bodies in Mammalia, *Quart. Journ. Micros. Sc.*, 1882.

[7] Quain's *Anatomy*, 9th edition. See also Klein's *Atlas of Histology*, p. 435.

suprarenals was found uniformly fatal, yet others"—for example, Phillipeaux—"have shown that this effect is rather attributable to hæmorrhage and the unavoidable injury to the nerves, and especially to the semilunar ganglia, attendant upon the operation, than, as Brown-Séquard believed, to the retention of some poisonous substance in the circulation, which it is the office of these bodies to remove." But of late Tizzoni has produced bronzing of skin and mucous membrane by artificially removing the adrenals, so that the above statement may be set aside. The idea that the adrenals are concerned in the elaboration of nutrient material is negatived by the result of chemical examination, and that of their being nervous ganglia by the results of recent studies on their development.

The view of Dr. Harley, lately supported by Spannochi,[8] that the adrenals are merely persistent fœtal structures—even if true—would prove nothing, nor add to our knowledge of their function in adult life. But we have on the other side the opinion of Professor Wiedersheim, who says: "Their extraordinary richness in blood vessels, which is seen throughout life, points to the important function of these organs; but it is impossible to say at present what that function is." Besides, the distribution of the lymphatics of the adrenals, which Klein has studied, shows that these vessels must be concerned in carrying away some product of the metabolic activity of the gland, as Klein, indeed, assumes, a view recently confirmed by Stilling,[9] who shows that the pigment formed in the adrenals is carried away by the lymphatics to those lymphatic glands which lie along their path.

The fact that the adrenals are relatively large in fœtal life—at the end of the third month as large as the kidneys—proves nothing. The thyroid gland is of relatively large size during fœtal life also; and although a remnant "of one or more diverticula of the ventral wall of the pharynx or floor of the mouth," and "an ancient glandular organ," speaking from a phylogenetic point of view, "the secretory function of which in relation to the alimentary canal was of great importance in the ancestors of existing vertebrates,"[10] yet we know it must be of importance physiologically, for its atrophy from disease or its extirpation surgically leads to the production of myxœdema.

We ought not to lose sight of the fact that during fœtal life the liver has to manufacture red blood-corpuscles, and as the adrenal seem to be supplementary to the liver in one, at least, of its functions even in adult life, it may possibly be concerned in fœtal life with the removal of certain waste products instead of the liver.

Results of Spectroscopic Examination.—When carrying out an investigation of the spectra of the organs and tissues of vertebrates and invertebrates, I came upon the interesting fact that the suprarenals show the presence of the bands of hæmochromogen or reduced hæmatin, which I found to be especially well-marked in their medulla. In man, dog, cat, rabbit, rat, guinea-pig, ox, and sheep the result was practically the same. Wherever I had previously detected hæmochromogen in the fluids or organs of the body it had been excretory. There was indeed one exception—namely, in a beetle *(Staphylinus olens);* as its testes seem to contain this substance mixed with hæmoglobin, but this fact does not bear on the matter under discussion. In the liver[11] and in the

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[8] *Gazz. degli Ospitali*, Nos. v and vi; *Lond. Med. Record*, vol. xiii, p. 102.

[9] "Zur Anatomie der Nebennieren," Virchow's *Archiv*, Band cix, Heft 2, p. 324.

[10] Wiedersheim, *loc. cit.*

[11] It also occurs, as I have proved, in the "bile" of snails, slugs, crayfish, and common limpet. *Proc. Roy. Soc.*, No. 226, 1883.

bile hæmochromogen had been detected previously by me; hence, when I found it in the adrenals, I concluded that here also it must be excretory. Moreover, the appearance of the spectra differed in some cases in such a manner as to lead me to conclude that the substance which was being changed into hæmochromogen was found in different stages of metabolism, and the bands of the latter were certainly made fainter when the blood-vessels of the animal were washed out with salt solution. I subsequently found that it is highly probable that not only hæmoglobin, but also the histohæmatins may furnish hæmochromogen; and one frequently can detect a histohæmatin, especially in the cortical part of the adrenals. Hence I drew the obvious conclusion that in the adrenals a downward metamorphosis of worn-out pigments—hæmoglobins and the histohæmatins—is taking place, and the function of these organs is to pick out of the circulation these worn-out or effete colouring matters with their accompanying proteids; for if the coloured constituent be present, so also must the proteid, which together originally built up the molecule of a hæmoglobin or a histohæmatin. If then the adrenals discharge this function, we ought to find evidence of the presence in the excretions of incompletely metabolised pigments, when these pigment-metabolising organs are unfitted by disease for the performance of their function. And that is exactly what is found. I have detected, by means of the spectroscope, in the urine of Addison's disease, such a pigment, which I named "urohæmatin,"[12] but, subsequently I changed its name to "urohæmatoporphyrin," since it is a kind, of hæmatoporphyrin. The urinary pigments traceable back to bile and hæmatin are two in number—namely, normal and febrile urobilin, but the above pigment is, as I have shown, produced only from hæmatin by the action of such reducing agents as zinc and sulphuric acid and sodium amalgam. In the JOURNAL for 1883 (December 1st) I showed that it occurs in the urine of acute rheumatism, but subsequent investigation has convinced me that it is present in various febrile conditions, and to sum the matter up, it may be said to be present in urine under at least two conditions: (1) when an excess of effete hæmoglobin or histohæmatin[13] is present in the circulation, the blood-metabolising glands being healthy, but incapable of dealing with the excess of effete pigment; or (2) when the amount of effete pigments may be not in excess, but the blood-metabolising glands are diseased. In the urine of cirrhosis of the liver, where the secretory cells are encroached upon by connective tissue, it is present, and in the urine of Hodgkin's disease, when the skin had become bronzed, owing to disease of the adrenals, it has been found. In a case of this kind Dr. Saundby actually labelled the specimen "urohæmatin," suspecting its presence from what I had told him, and it was present. In Addison's disease I have found it several times. In the later stages of that disease, when the blood has become deteriorated from the presence in it of various poisonous products of incomplete metamorphosis, of course we may have to acknowledge two sources of this urohæmatoporphyrin—namely, effete pigment present from disease of the adrenals, and effete pigment due to subsequent excessive destruction of the red blood-corpuscles. In many cases the simple addition of a mineral acid to the urine will bring out the bands of

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12 *Proc. Roy. Soc.*, vol. xxxi, p. 26, and vol. xxxv, p. 394; *Journ. Physiol.*, vol. vi, p. 22, *et seq.*

13 Hæmatoporphyrin is present in the integument of invertebrates in which no hæmoglobin can be found. (See *Jour. Physiol.*, vol. vii, No. 3, and vol. viii, No. 6.) Hence, and since it can be artificially prepared from myohæmatin, I concluded it might be a metabolite of the histohæmatins.

acid urohæmatoporphyrin; in other cases it may be necessary to precipitate the urine with neutral and basic acetate of lead, decompose the precipitate with rectified spirit acidulated with sulphuric acid, and filter; this filtrate then shows the bands of acid urohæmatoporphyrin well marked, and from this it can be isolated by agitation with chloroform, as I have elsewhere described. C. Nobel has lately confirmed my conclusions with regard to this pigment, and proposes calling it "isohæmatoporphyrin."[14] Its presence, however, in the urine lends support of a substantial kind to my theory, and teaches that, other conditions being absent, it may be due to disease of the blood-metabolising glands; and since in many cases where I have found it the only glands diseased were the adrenals, these must be blood-metabolising glands.

The discovery by Krukenberg[15] of the presence of pyrocatechin, or a nearly related substance, in the alcohol extract of the adrenals of herbivorous animals, has led some to suppose that his results contradict mine. Krukenberg never said so; he only stated that it was incomprehensible to him that I should have found hæmochromogen in perfectly fresh organs, but he does not deny its occurrence. It must be remembered, as Krukenberg himself says, that several chromogens are present in the adrenals, and the one which Krukenberg investigated was soluble in alcohol, whereas hæmochromogen is not. Possibly the adrenals of carnivora may not contain pyrocatechin, for in the blood serum of herbivora and in their urine various "aromatic" substances are present which, as Hoppe-Seyler has shown, are peculiar to them; but even if present in the adrenals of flesh-eating animals, it would lend support to my theory. We know that other aromatic bodies such as indol, skatol, kresol, etc., are produced from proteids by the action of ferments; and although putrefaction seems necessary for the production of some, yet with our present knowledge we cannot say that they are not produced within the body in the absence of putrefaction; indeed, skatol does not owe its increased production in diabetics, in all probability, to putrefaction. Therefore, the presence of pyrocatechin in the adrenals would merely show that proteid metabolism is taking place there, which is one of the points I wish to prove.

Teachings of Pathology and General Summary.—I do not propose considering the question whether there is a specific disease of the adrenal, such as a "strumous" or tuberculous condition present in that class of cases known now as Addison's disease, or whether Dr. Addison wished after he had published his views to narrow the pathology of that disease to disease of the sympathetic ganglia.[16] Because many believe with Virchow that the peculiar train of symptoms with bronzing of the skin, which are characteristic of Addison's disease, may be brought about by various morbid conditions of the adrenals, and a perusal of recently recorded cases shows that we must extend our view so as to include such morbid conditions. Nor should I consider the occurrence of diseased adrenals without bronzing of the skin, or bronzing of the skin without disease of these organs,

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[14] *Chem. Centralblatt*, 1887, p. 538. Original in *Arch. f. d. Ges. Physiol.*, xl., 11 and 12, p. 501.

[15] Virchow's *Archiv.*, 101 Band, 1885, s. 542-571, Krukenberg describes some chromogens got by the artificial digestion of fibrin which bear some resemblance to those of the adrenal, but are different. "Zur Charakteristik, etc.," *Verh. der Phys. Med. Gesell. z. Würzburg*, 1884, band 18, No. 9.

[16] See Dr. Goodhart's able summary in New Sydenham's Society's *Atlas of Pathology*, and compare Addison's works, New Sydenham Society's edition, 1868, p. 214.

an argument against the theory adopted here, because the adrenals being supplementary organs, other organs may do duty for them to a great extent, under certain unknown conditions. Besides, if Addison's disease were to occur in a patient in whom by previous disease the hæmoglobins and the histohæmatins had been diminished in amount, we should not expect to meet with much effete pigment in that case.[17] And even if the adrenals are apparently healthy, we cannot always say whether there has not been some interference with their nervous or arterial supply sufficient to prevent the discharge of their functions. Looking over the recent literature of this subject, one finds some very interesting cases of Addison's disease described. In the case recorded by Dr. Wickham Legg,[18] there were shortness of breath, giddiness and vomiting, bronzing of skin, and paroxysm of fever. In Monti's [19] case there were several febrile attacks during the course of the case, drowsiness and heavy sleeps, excitement, delirium, and loss of consciousness, and death took place in a convulsion. In Rauschenbach's[20] case there were rigors and "heat" at the beginning of the illness, restlessness, delirium, and various nervous symptoms. In Cacciola's[21] case febrile attacks were also noticed, and the patient became delirious before death, and died in a convulsion.

In some of these cases the nervous symptoms and the hyperthermia are very remarkable (especially as it has been said the temperature is subnormal in Addison's disease, which is a very doubtful statement), and these symptoms are explicable only on the assumption that some toxic substance or substances must have been present in the blood. That such is the case seems more than probable from the experiments of Foa and Pellacani,[22] which have not met with the attention which they deserve. These observers injected an aqueous filtered extract from certain organs, namely, the brain, the testis, and the adrenals, into the veins of rabbits, and found that death ensued, which was due to coagulation of the blood in the heart and lesser circulation. They proved that a fibrinogenous ferment, both chemically and physiologically active, was present in the solutions, which is due not to the blood circulating in these organs, nor to destruction of white corpuscles in them, but to a substance present in the organs; and when the solutions injected were little active, marasmus was produced, from which the animal died. But here is the most important result; they found that aqueous and alcohol extracts of the adrenals had a most toxic effect, an effect peculiar to the extracts of these organs. The poison present in the adrenals is more like an organic acid or a "ptomatin" in its action; it paralyses the spinal cord, etc., and causes death by paralysing the "bulbar centre," and especially the respiratory centre. Is this, then, the product of proteid disintegration which it is the province of the adrenals to pick out of the circulation and metabolise into a harmless substance, and which, when these organs are diseased, accumulates in the blood, and produces nervous symptoms and hyperthermia; for Foa and Pellacani found that it also produced increase of temperature?

We know that the poisonous alkaloids of animal origin, the

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17 In the adrenals from a case of pernicious anæmia sent me by Dr. W. Russell, of Edinburgh, the bands were extremely faint.

18 *Lancet*, June, 1885, p. 1027. *Med. Rec.*, vol. xiii.

19 *Archiv für Kinderheilkunde*, Band vi, Heft. 4.

20 *Vratch*, No. 1, 1886.

21 *Gazz. Med. Ital. Prov. Venet.*, No. 5, 1884; *Giornale Internaz. delle Sci. Med. Fasc*, viii. 1884.

22 *Arch. per. le Sc. Med.*, vii, 9, 1885; and Schmidt's *Jahrbücher*, Band 210, 1886.

ptomaines and leucomaines,[23] are products of "proteid disintegration." The poison of the adrenals is, however, probably neither the one nor the other, but a nitrogenous, non-crystallisable substance akin to Panum's septic poison; such bodies produce hyperthermia, whereas the ptomaines and leucomaines produce hypothermia. The bodies which are nearer proteids, or themselves of a proteid nature, appear to be even more poisonous than their lower metabolites. As is well known, Wooldridge[24] obtained a proteid poison from serum which prevents shed blood from coagulating for several hours; and another proteid poison[25] from the testis and thymus of the calf, which, injected into the blood vessels of an animal, causes instant death, due to wide-spread intravascular clotting. Wolfenden,[26] too, has shown that the poison of the Indian cobra *(Naja tripudians)* and the Indian viper are of a proteid nature.

The presence of urohæmatoporphyrin in the urine of Addison's disease led me to hope that I should find this or some other metabolite of hæmoglobin in the skin of patients sufficiently bronzed for the examination, but in this I have been disappointed. Professor Victor Horsley and Dr. Dingley kindly procured some skin, and the latter some slate-coloured mucous membrane from the mouth, from patients suffering from Addison's disease; but although I detected traces of iron, I could not see any bands. But this is not surprising, seeing how quickly blood becomes altered in those situations.

Dr. Riehl[27] and Dr. Ernest Kummer[28] have made some observations on the distribution of pigment in the skin in these cases. Dr. Riehl concludes that the pigment is extracted from the blood by the cutis cells, and that it is not produced *in situ* by metabolic processes in the cells of the rete; he also found thrombi in the blood vessels of the skin. Kummer confirmed these results, and thinks that we may assume a disease of the blood as a cause of Addison's disease. But it seems to me that the pigment primarily deposited in the skin is different in its origin from that deposited later, when the blood itself has become deteriorated from the presence in it of the products of incomplete metamorphosis. It is interesting to compare with Dr. Riehl's statement that of Wiedersheim[29] on the pigmentation of the skin of lower vertebrates; he shows that the derma is permeated by leucocytes, especially in fishes. These leucocytes penetrate to the superficial layer of the epidermis, and carry pigment granules. Here they take on amœboid movements, and break up into numerous small, pigment-containing particles, which are taken up by the epithelial cells.

It would appear, then, that comparative anatomy and comparative embryology, physiological chemistry, the evidence supplied by the spectroscope and by pathology, all point to the same conclusion.

Just as there has been a progressive development of vertebrata in time, the fishes appearing in the upper silurian, the reptiles in the carboniferous, the birds in the triassic, and mammals in the jurassic, or even in the triassic systems,[30] so has there been a progressive development in their organs. As

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[23] *Cf.* A. M. Brown, *A Treatise on the Animal Alkaloids*, 1887; also Sir W. Aitken's little volume on the same subject.
[24] *Proc. Roy. Soc.*, xlii, 230-232.
[25] *Ibid.*, xl, 134-135.
[26] *Journ. Physiol.*, vii, 327-370.
[27] *Zeitschr. f. Klin. Med.*, x, 5 and 6.
[28] *Corr. Bl. f. Schweiz. Aerzte*, xvi, 15, 16, 1886.
[29] *Comp. Anat. Vertebrates*, Eng. trans., p. 16.
[30] Geikie's *Textbook of Geology*, p. 664, 2nd ed., 1885.

the animal body became more complex, and a greater abundance of respiratory pigments had become necessary for internal and ordinary respiration, certain organs had to be set apart, or had to take on a new function, in the increased "division of labour." This function in the case of the adrenals was the removal from the circulation of useless and worn-out pigments and their accompanying proteids.[31]

When the adrenals are diseased, these effete pigments and effete proteids circulate in the blood; the former, or their incomplete metabolites, producing pigmentation of skin and mucous membrane, and appearing often in the urine as urohæmatoporphyrin; the latter producing toxic effects, and leading to further deterioration of the blood with its consequences.

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[31] *Philos. Trans.*, Part I, 1886.